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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/644,055	08/19/2003	Paul A. Barsanti	19099.004	5144

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EXAMINER	
SEAMAN, D MARGARET M	
ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/644,055	BARSANTI ET AL.	
	Examiner	Art Unit	
	/D. Margaret Seaman/	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42,43,52 and 69-92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42,43,52 and 69-92* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application was filed 8/19/2003. Claims 42-43, 52, 69-92 are before the Examiner.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. The rejection of claims 42-43 and 52 and now claims 69-92 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained. As previously stated, the claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant specification does not adequately describe the nexus between the modulation of the specific tyrosine kinases (i.e. c-Kit among others and a useful treatment of a disease/condition. Modulation of a receptor involves antagonism, inhibition, agonism and others. These modulations are sometimes opposite reactions to the same receptor. Further, claims directed to mediating a biological pathway are devoid of identifiable utility and are therefore not useful. Unless the pathway as issue is critical to treating some condition and the pathway modification and disease

treatment are inexorably linked, such pathway modification is devoid of utility. Since, the claims as recited embrace any degree of inhibition of tyrosine kinase c-Kit and other specific tyrosine kinases , which may or may not be inexorably linked to the treatment of any disease, the scope of the claims is therefore not commensurate with the objective enablement in absence of a full written description of the as yet unidentified condition/activities/ disorders which the recited mechanism reaches out to. It is not seen where the instant specification adequately describes the nexus between the modulation of the c-Kit tyrosine kinase receptor and a useful treatment of a single disease or condition.

Applicants argue that the instant claims meet the written description requirement because each kinase plays a critical role in one or more disorders and that each of the tyrosine kinases are known to mediate or otherwise contribute to a variety of disorders. However, applicant has not provided a nexus between the activity at the cellular level with a real world treatment. It is well known that kinases are involved in just about everything that the body is involved in. However, getting from an activity of inhibiting (or mediating) kinases to the real world treatment of cancer (specifically or generically) has not been described by the instant specification. The art does not accept that any compound that mediates kinase would automatically treat cancer. Due to this, the rejection is maintained.

3. The rejection of claims 42-43 and 52 and now claims 69-92 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, as stated in office action dated 9/2006, is maintained. As previously stated, the claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

1) The breadth of the claims,
2) The nature of the invention,
3) The state of the prior art,
4) The level of one of ordinary skill,
5) The level of predictability in the art,
6) The amount of direction provided by the inventor,
7) The existence of working examples,
8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The nature of the invention: The nature of the invention is the method of treating a disorder that is modulated by the tyrosine kinase receptor c-Kit, C-ABL and others.

The state of the prior art: The state of the prior art is that it involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells

from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, claims directed to mediating a biological pathway are devoid of identifiable utility and are therefore not useful. Unless the pathway as issue is critical to treating some condition and the pathway modification and disease treatment are inexorably linked, such pathway modification is devoid of utility. Since, the claims as recited embrace any degree of inhibition of tyrosine kinase c-Kit and other specific tyrosine kinases , which may or may not be inexorably linked to the treatment of any disease, the scope of the claims is therefore not commensurate with the objective enablement in absence of a full written description of the as yet unidentified condition/activities/ disorders which the recited mechanism reaches out to. One of ordinary skill in the art therefore would not be able to use the inventive compound as claimed without undue experimentation.

The predictability in the art: It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In

the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to the therapeutic effects of all diseases, whether or not the modulation of tyrosine kinase c-Kit or other specific tyrosine kinase receptors would make a difference in the disease. Hence, in the absence of a showing of a nexus between any and all known diseases and the modulation of a specific tyrosine kinase receptor, one of ordinary skill in the art is unable to fully predict possible results from the administration of the compound of claim 1 due to the unpredictability of the role of modulation of tyrosine kinase specific receptors.

The presence or absence of working examples: The specification describes many tests. However, it is not seen where the instant specification describes a test that shows the instant compounds inhibiting a specific tyrosine kinase above inhibiting all or some or most of the tyrosine kinases.

The amount of direction or guidance present: The guidance present in the specification is that of the compounds work. The specification states that tyrosine kinases are thought to play an important role in a variety of diseases. Also, the biological effects of kinins are mediated through many different and specific tyrosine kinase receptor subtypes. The specification does not seem to enable a correlation between the mediation of specific tyrosine kinase receptors and the treatment of any and all diseases.

The breadth of the claims: The claims are drawn to the treatment of any and all diseases mediated by the tyrosine kinase receptor with the compounds.

The quantity of experimentation needed: The quantity of experimentation needed is undue. One skilled in the art would need to determine what diseases out of all known diseases would be benefited by the mediation of tyrosine kinase receptors and then would further need to determine which of the claimed compounds would provide treatment of the disease.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compounds of claim 1 for the treatment of any disease. As a result necessitating one of ordinary skill to perform an exhaustive search for which diseases can be treated by which compound of claim 1 in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, one of ordinary skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compounds of the instant claims, with no assurance of success.

This rejection can be overcome by deleting the claims.

Applicant argues that the instant claims are not drawn to the treatment of any and all diseases mediated by tyrosine kinase receptor. However, claim 42 and all claims dependent from claim 42 are drawn to inhibiting a tyrosine kinase in a subject. This infers that something is being treated pharmacologically in that subject without saying what is being treated. Due to this, it is inferred that anything and everything that can be treated by a tyrosine kinase inhibitor is being treated. The new claims are drawn to a method of treating all cancers.

Applicant argues that the level of predictability in the art supports the instant methods. However, as shown above, the art does not support the treatment of cancer by the in vitro showing of treating specific cancers in several specific cancer cell lines. The level of predictability is extremely low in this art. Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled

conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, although drawn specifically to cancer cells, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not.

Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Applicant argues that the working examples provided in the instant specification show that the instant compounds will treat cancer in vivo. However, as shown above, in vitro testing for cancer treatment in multiple cancer cell lines is not accepted as predictive of in vivo activity.

Taking this all into consideration, the rejection of claims 42-43, 52 and 69-92 is upheld.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States

only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. The rejection of claims 42-43 and 52 and now 69-92 under 35 U.S.C. 102(e) as being anticipated by Renhowe (US Patent 6605617 and 6800760), is upheld. Renhowe claims a method of treating a patient in need thereof of an inhibitor of tyrosine kinase using a quinolinone derivative that covers the instantly claimed composition. The new claims 83-92 encompass inhibiting any and all tyrosine kinases.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

6. Claims 42-43 and 52and now claims 69-92 remain rejected under 35 U.S.C. 102(a) as being anticipated by Renhowe (US Patent 6605617 and WO 2002/0107392 A1 and WO 200222895). Renhowe teaches a method of treating a patient in need thereof of an inhibitor of tyrosine kinase using a quinolinone derivative that covers the instantly claimed composition.

Applicant argues that since the art cited does not specify which tyrosine kinase is being inhibited, that the prior art does not encompass the instant claims. Claims 83-92 do not limit the claims by specifying a specific tyrosine kinase. The art inhibits tyrosine kinases. This encompasses any and all known tyrosine kinases, since that was the state of the art at the time the articles were written. If applicant has evidence that the tyrosine kinases referred to in the prior art cited above was a tyrosine kinase different than is instantly claimed, then applicant is welcome to supply such evidence.

Conclusion

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to /D. Margaret Seaman/ whose telephone number is 571-272-0694. The examiner can normally be reached on 730am-4pm, Monday-Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thomas McKenzie can be reached on 571-272-0670. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/D. Margaret Seaman/
Primary Examiner
Art Unit 1625

dms